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Aortic arch calcification affects causes of death in patients on hemodialysis: a retrospective cohort study

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Abstract

Background: Aortic arch calcification (AAC) is a well-known risk factor for death in patients on hemodialysis (HD); however, the causes of death among them have not been well studied. The study aimed to investigate the distribution of causes of death and long-term prognosis among different degrees of AAC in HD patients.

Methods: A retrospective cohort study was conducted on patients undergoing HD at two clinics in Japan. AAC grades 0 to 3 were categorized by chest radiograph at baseline, and mortality and causes of death were collected. A subgroup analysis was performed to evaluate the relationship between causes of death and age, diabetes mellitus, and dialysis vintage in each AAC grade.

Results: A total of 321 patients were included in the analysis. During 5.2 ± 2.1 years, 117 patients died, and the death rates in AAC grades 0, 1, 2, and 3 were 19.3% (17/88), 35.2% (51/145), 46.3% (25/54), and 70.6% (24/34), respectively. The major causes of death were cardiovascular disease (CVD, 39.3%), infection (20.5%), and malignancy (15.4%) in the entire cohort. In AAC grade 3, CVD mortality (33.3%) remains as the most common cause of death, although death of infection (29.2%) and malnutrition (16.7%) increased markedly. A subgroup analysis showed that AAC grade 3 was mostly old, non-diabetic patients with a long dialysis vintage and was susceptible to death of infection or malnutrition.

Conclusions: CVD was the most common cause of death among all AAC grades, although death of infection and malnutrition markedly increased in those with severe AAC. Attention should be paid to CVD, infection, and malnutrition in HD patients with severe AAC.

Keywords: Cause of death, End-stage kidney disease, Malnutrition, Mortality, Vascular calcification

Background

Aortic arch calcification (AAC) in chest radiograph has been reported as a risk factor for morbidity and mortality in patients on hemodialysis (HD). Previous studies have shown that the grade of AAC was associated with death from any cause and cardiovascular diseases (CVD) in HD patients [1–3]. A recent meta-analysis on eight cohort studies on HD patients revealed that AAC has resulted in a 44% and 130% increase in all-cause mortality and CVD death, respectively [4]. While a previous report showed that AAC was also a significant predictor of all-cause mortality and CVD death in patients with non-dialysis dependent chronic kidney disease (CKD), vascular calcification was more apparent in patients on HD than those with non-dialysis dependent CKD [5].

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CVD is the leading cause of death among HD patients worldwide [6]. In Japan, the major causes of death in patients on maintenance dialysis were CVD (33.1%) followed by infection (21.3%) and malignancy (8.4%), according to the annual reports from the Japanese Society for Dialysis Therapy (JSDT) [7]. Dialysis patients often show advanced vascular calcification which may contribute to CVD death in HD patients. However, the impact of AAC on causes of death in HD patients with severe AAC has not been well studied. Reporting the cause of death among different degrees of AAC should be useful for recognizing what clinician should pay an attention in clinical practice among patients on HD.

This study aimed to clarify the distribution of causes of death and long-term prognosis among different AAC grades in patients on HD.

Methods

Patients

A retrospective observational study was conducted on Japanese HD patients from two HD clinics. As our previous study [8], we recruited 366 patients who were treated on maintenance HD therapy in Shinkoiwa Clinic and Shinkoiwa Clinic Funabori, Tokyo, Japan, between January and March 2012. Forty-five patients were then excluded because of deficits of clinical parameters. Finally, 321 patients were enrolled in this study and were followed until the end of 2018, renal transplantation, or loss to follow-up. The main outcome of this study was the difference in causes of death by AAC grades. All-cause mortality and CVD death rate by AAC grades were also examined.

AAC grading

AAC in chest radiograph at baseline was classified into four grades by two independent nephrologists. The definition of AAC grades was described elsewhere [9]. Briefly, grade 0 indicated no visible calcification, grade 1 indicated small spots of calcification or single thin calcification of the aortic knob, grade 2 indicated one or more areas of thick calcification, and grade 3 indicated circular calcification of the aortic knob.

Data collection

All baseline data were collected from medical records. Baseline data included age, sex, hypertension, diabetes mellitus (DM), ischemic heart disease, stroke, hemoglobin, corrected serum calcium, serum phosphorus, albumin, C-reactive protein, alkaline phosphatase, magnesium and intact parathyroid hormone, and use of $CaCO_3$, Ca-free phosphate binders, and vitamin D3. Hypertension was defined as blood pressure greater than 140/90 mmHg, use of antihypertensive agents, or those having its medical history at baseline. DM was defined as the use of anti-glycemic agents or those with its medical history at baseline.

Causes of death were based on the report of the death certificate and medical records. CVD included sudden cardiac death, ischemic heart disease, heart failure, peripheral arterial disease, and stroke. Natural death of old age/frailty was included in death of malnutrition. Deaths with no reported cause were categorized as missing [10].

Statistical analysis

Values were expressed as mean ± standard deviation or median (interquartile range), as appropriate. A comparison of continuous variables among all AAC groups was performed using the ANOVA. Categorical data were compared using the Fisher's exact test. The Kaplan–Meier method with censoring for renal transplantations or loss to follow-up was used to estimate the probabilities of death from any cause and CVD death and was statistically tested with the log-rank test. Variables relevant to all-cause mortality were identified by the univariate Cox proportional hazard models. Multivariate Cox proportional hazard analyses were performed using two models: Model 1 included all significant variables in the univariate analyses, and Model 2 included statistically relevant variables using a backward stepwise method. To clarify the factors related to causes of death, a subgroup analysis of causes of death was conducted using age, primary disease of end-stage kidney disease (ESKD), and dialysis vintage as a factor in each AAC grade.

As this was an exploratory analysis, we considered p values < 0.05 as statistically significant. All statistical tests were performed using JMP 13.0.0 (SAS Institute Inc., Cary, North Carolina, USA).

Results

A total of 321 patients were included in the analysis. The mean age at baseline was 64 ± 11 years, and 65.7% were male, and the mean dialysis vintage was 10 ± 8 years. AAC grades 0, 1, 2, and 3 were identified in 88 (27.4%), 145 (45.2%), 54 (16.8%), and 34 (10.6%) patients, respectively (Table 1). The patients with higher AAC grades were older and had a longer dialysis vintage and showed lower serum albumin levels than those with lower AAC grades. The prevalence of hypertension, DM, and the use of $CaCO_3$ was lower in patients with AAC grade 3 than those with AAC grades 0 to 2.

During the mean observation period of 5.2 ± 2.1 years, 117 (36.4%) patients died from any cause. All-cause mortality increased in accordance with the increase in AAC grade ($p < 0.001$), and the death rates during the follow-up period in AAC grades 0, 1, 2,

Table 1 Baseline characteristics of the participants by aortic arch calcification grade

Variable	All N = 321	Grade 0 N = 88	Grade 1 N = 145	Grade 2 N = 54	Grade 3 N = 34	*p* value
Age (year)	64 ± 11	57 ± 11	65 ± 11	66 ± 8	73 ± 7	**< .001**
Male, n (%)	211 (65.7)	59 (67.1)	100 (69.0)	29 (53.7)	23 (67.7)	0.245
Dialysis vintage (year)	9.7 ± 8.2	8.2 ± 7.4	9.3 ± 8.0	12.8 ± 9.1	10.8 ± 8.5	**0.010**
Diabetes, n (%)	131 (40.8)	45 (51.1)	56 (38.6)	24 (44.4)	6 (17.7)	**0.006**
Hypertension, n (%)	177 (55.1)	41 (46.6)	91 (62.8)	31 (57.4)	14 (41.2)	**0.032**
Ischemic heart disease, n (%)	65 (20.3)	14 (15.9)	31 (21.4)	16 (29.6)	4 (11.8)	0.148
Stroke, n (%)	84 (26.2)	17 (19.3)	35 (24.1)	20 (37.0)	12 (35.3)	**0.064**
Serum albumin (g/dL)	3.7 ± 0.3	3.7 ± 0.3	3.7 ± 0.3	3.6 ± 0.3	3.4 ± 0.3	**< .001**
Hemoglobin (g/dL)	10.0 ± 0.9	10.2 ± 0.9	9.9 ± 0.8	10.0 ± 1.0	9.9 ± 0.9	0.108
C-reactive protein (mg/dL)	0.1 (0.0–0.3)	0.1 (0.0–0.3)	0.1 (0.0–0.4)	0.1 (0.0–0.2)	0.2 (0.0–0.4)	0.525
Corrected serum calcium (mg/dL)	9.2 ± 0.5	9.1 ± 0.6	9.2 ± 0.5	9.2 ± 0.5	9.4 ± 0.5	0.120
Serum phosphorus (mg/dL)	5.9 ± 1.3	6.0 ± 1.5	5.9 ± 1.3	5.8 ± 1.2	5.8 ± 1.0	0.712
Alkaline phosphatase (U/L)	252 ± 7	252 ± 14	248 ± 11	267 ± 17	250 ± 22	0.829
Magnesium (mg/dL)	2.6 ± 0.02	2.6 ± 0.04	2.6 ± 0.03	2.6 ± 0.1	2.5 ± 0.1	0.308
Intact parathyroid hormone (pg/mL)	177 ± 7	186 ± 14	165 ± 11	184 ± 18	195 ± 22	0.467
Use of $CaCO_3$, n (%)	209 (65.3)	61 (70.1)	99 (68.3)	34 (63.0)	15 (44.1)	**0.045**
Use of Ca-free phosphate binders, n (%)	179 (55.9)	53 (60.9)	80 (55%)	28 (51.9)	18 (52.9)	0.705
Use of vitamin D3, n (%)	117 (36.6)	30 (34.5)	57 (39.3)	18 (33.3)	12 (35.3)	0.840

AAC, aortic arch calcification

Values are expressed as mean ± standard deviation or median (interquartile range). Values in boldface type are significant ($p < .05$)

and 3 were 19.3%, 35.2%, 46.3%, and 70.6%, respectively (Fig. 1a). CVD mortality was also higher in patients with higher AAC grades than those with lower grades (p = 0.011) (Fig. 1b). Univariate analyses showed that AAC grades 1 to 3, age, ischemic heart disease, stroke, serum albumin, hemoglobin, C-reactive protein, use of Ca-free phosphate binders, alkaline phosphatase, and serum magnesium were the significant variables for all-cause mortality (Table 2). On a multivariate analysis, grade 3 AAC remains a significant risk factor for all-cause mortality, even after adjustment for all significant variables in univariate analysis (Table 3, Model 1). Further, the association between grade 3 AAC and all-cause mortality remained significant in another Cox proportinal hazard model using a backward stepwise method (Table 3, Model 2).

CVD was the most common cause of death among all AAC grades (Fig. 2). The major causes of death were CVD (39.3%), infection (20.5%), and malignancy (15.4%) in the entire cohort. In AAC grade 3, CVD mortality (33.3%) remains as the most common cause of death, although death of infection (29.2%) and malnutrition (16.7%) increased markedly. Among CVD death, sudden cardiac death (14.5%), stroke (10.3%), and heart failure (9.4%) were the major causes in the entire cohort. However, in patients with AAC grade 3, stroke was the most common cause of death and accounted for 16.7% of total death, which was mostly due to an increase in cerebral infarction. AAC grades did not alter the proportion of CVD death for total death in our cohort.

A subgroup analysis showed that most patients who died from infection or malnutrition were elderly and non-DM (Table 4). These trends became more apparent in patients with higher AAC grades. Further, an increase in mortality from infection and malnutrition was observed in patients with a long dialysis vintage in severe AAC grade.

Discussion

This study showed that CVD was the most common cause of death among all AAC grades in HD patients, while death of infection and malnutrition markedly increased in those with severe AAC. AAC was associated with all-cause and CVD mortality. These findings confirm that CVD is the primary issue of healthcare in patients on HD [6, 11] and highlight the importance of paying more attention to the occurrence of fatal infection and the management of nutrition in HD patients with severe AAC.

In this study, CVD was the most common cause of death in HD patients with all AAC grades. A previous study showed that CVD mortality accounted for 37.7% of total death in patients with severe AAC, and those rates by AAC grades 0, 1, 2, and 3 were 5.3%, 12.7%, 18.9%, and 24.4%, respectively [3]. In this study, CVD mortality was 39.3% in entire cohort; however, there

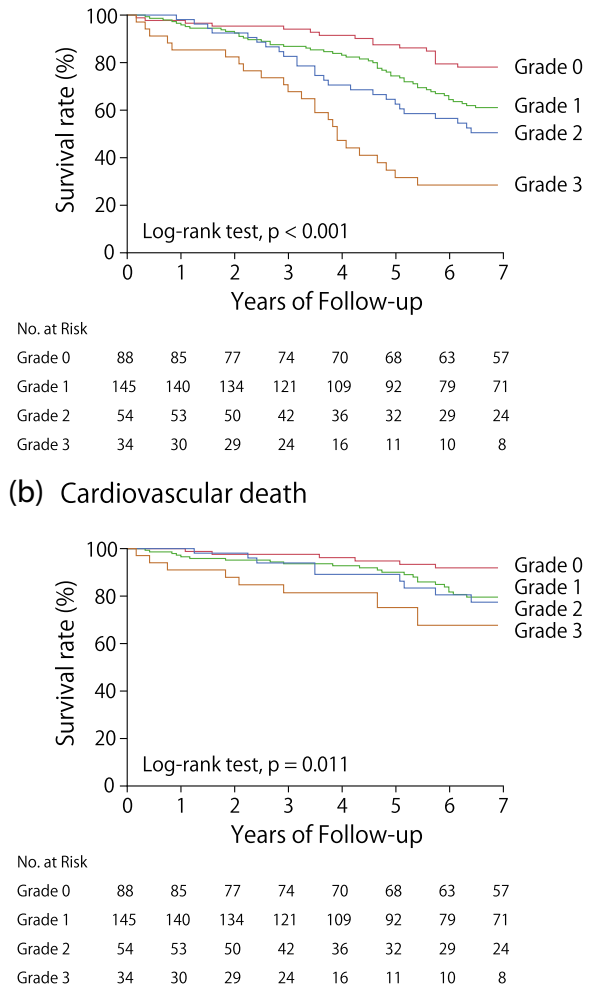

Fig. 1 Kaplan–Meier analysis for all-cause mortality and cardiovascular death. Shown are the Kaplan–Meier analysis for (**a**) death from any cause and (**b**) CVD death by AAC grades among patients on HD. The table reported in this figure shows the number of at-risk patients. All-cause mortality and CVD death rates were significantly higher in patients with higher AAC grades. AAC, aortic arch calcification; CVD, cardiovascular disease; HD, hemodialysis

was no clear difference in CVD mortality among AAC grades. The low prevalence of DM, a well-known poor prognostic factor [12], may also have influenced no increase in CVD mortality in our patients with severe AAC. Of note, ischemic stroke mortality tended to occur more frequently in severe AAC group in this study. This finding was compatible with a previous report that the incidence of cerebral infarction was associated with advanced calcification of the thoracic aorta [13]. Our findings show that CVD is a critical issue regardless of AAC grades in patients on HD.

Table 2 Univariate Cox proportional hazard analysis for all-cause mortality

Variable	HR	95% CI	*p* value
AAC grade 1*	1.98	1.14—3.42	**0.015**
AAC grade 2*	2.78	1.50—5.15	**0.001**
AAC grade 3*	5.72	3.06—10.7	**<.001**
Age (10 years)	1.85	1.55—2.22	**<.001**
Male	0.74	0.51—1.06	0.101
Dialysis vintage (year)	1.02	0.99—1.04	0.168
Diabetes	1.28	0.88—1.84	0.222
Hypertension	1.13	0.79—1.64	0.497
Ischemic heart disease	1.79	1.19—2.69	**0.005**
Stroke	1.81	1.24—2.66	**0.002**
Corrected serum calcium (mg/dL)	0.99	0.70—1.41	0.968
Serum phosphorus (mg/dL)	0.88	0.76—1.01	0.078
Serum albumin (g/dL)	0.18	0.10—0.34	**<.001**
Hemoglobin (g/dL)	0.77	0.62—0.94	**0.011**
C-reactive protein (mg/dL)	1.44	1.22—1.66	**<.001**
Alkaline phosphatase (U/L)	1.00	1.00—1.00	**<.001**
Magnesium (mg/dL)	0.37	0.22—0.62	**<.001**
Intact parathyroid hormone (pg/mL)	1.00	1.00—1.00	0.925
Use of $CaCO_3$	0.70	0.48—1.00	0.053
Use of Ca-free phosphate binders	0.63	0.44—0.91	**0.013**
Use of vitamin D3	0.99	0.68—1.45	0.972

AAC, aortic arch calcification; HR, hazard ratio; CI, confidence interval

*AAC grade 0 was used as reference. Values in boldface type are significant ($p < .05$)

We found that death of infection and malnutrition markedly increased in HD patients with severe AAC. Previous studies reported that elderly HD patients are susceptible to malnutrition, inflammation, and atherosclerosis syndrome that was associated with AAC progression [14–16] and elevated mortality in dialysis patients [17]. Further, it has been reported that elderly HD patients often died of infectious diseases, including pneumonia and sepsis [18]. In our study, an increase in mortality from infection and malnutrition was observed in elderly and non-DM patients with a long dialysis vintage in severe AAC grade. This finding suggests that patients with higher AAC grades were related to old age, non-DM, and long dialysis vintage and were more susceptible to death of infection and malnutrition.

The usefulness of AAC assessment has been reported in many previous studies mainly based on the association between AAC and mortality [2–4], although a recent study noted that AAC did not provide additional information on the prediction of mortality beyond the routine clinical assessment [19]. Our analysis added evidence that the causes of death in patients on HD differ among different AAC severities.

Table 3 Multivariate analysis for all-cause mortality

Variable	Model 1			Model 2		
	HR	95% CI	*p* value	HR	95% CI	*p* value
AAC grade 1*	1.37	0.78—2.42	0.274	–	–	–
AAC grade 2*	1.83	0.97—3.43	0.061	–	–	–
AAC grade 3*	3.05	1.54—6.00	**0.001**	2.27	1.40—3.68	**<.001**
Age (10 years)	1.56	1.24—1.96	**<.001**	1.62	1.33—1.99	**<.001**
Ischemic heart disease	1.59	1.04—2.43	**0.033**	1.57	1.03—2.37	**0.034**
Stroke	1.48	0.99—2.22	0.053	1.51	1.02—2.24	**0.040**
Serum albumin (g/dL)	0.68	0.33—1.42	0.311	–	–	–
Hemoglobin (g/dL)	0.88	0.70—1.11	0.278	–	–	–
C-reactive protein (mg/dL)	1.12	0.92—1.36	0.235	1.18	0.97—1.42	0.084
Alkaline Phosphatase (U/L)	1.00	1.00—1.00	**0.003**	1.00	1.00—1.00	**0.005**
Magnesium (mg/dL)	0.57	0.31—1.05	0.071	0.54	0.30—0.96	**0.035**
Use of Ca-free phosphate binders	1.14	0.76—1.72	0.517	–	–	–

*AAC grade 0 was used as reference. Values in boldface type are significant ($p < .05$)

Multivariate Cox proportional hazard analyses were performed using two models: Model 1 included all significant variables in the univariate analyses, and Model 2 included relevant variables using backward stepwise method

AAC, aortic arch calcification; HR, hazard ratio; CI, confidence interval

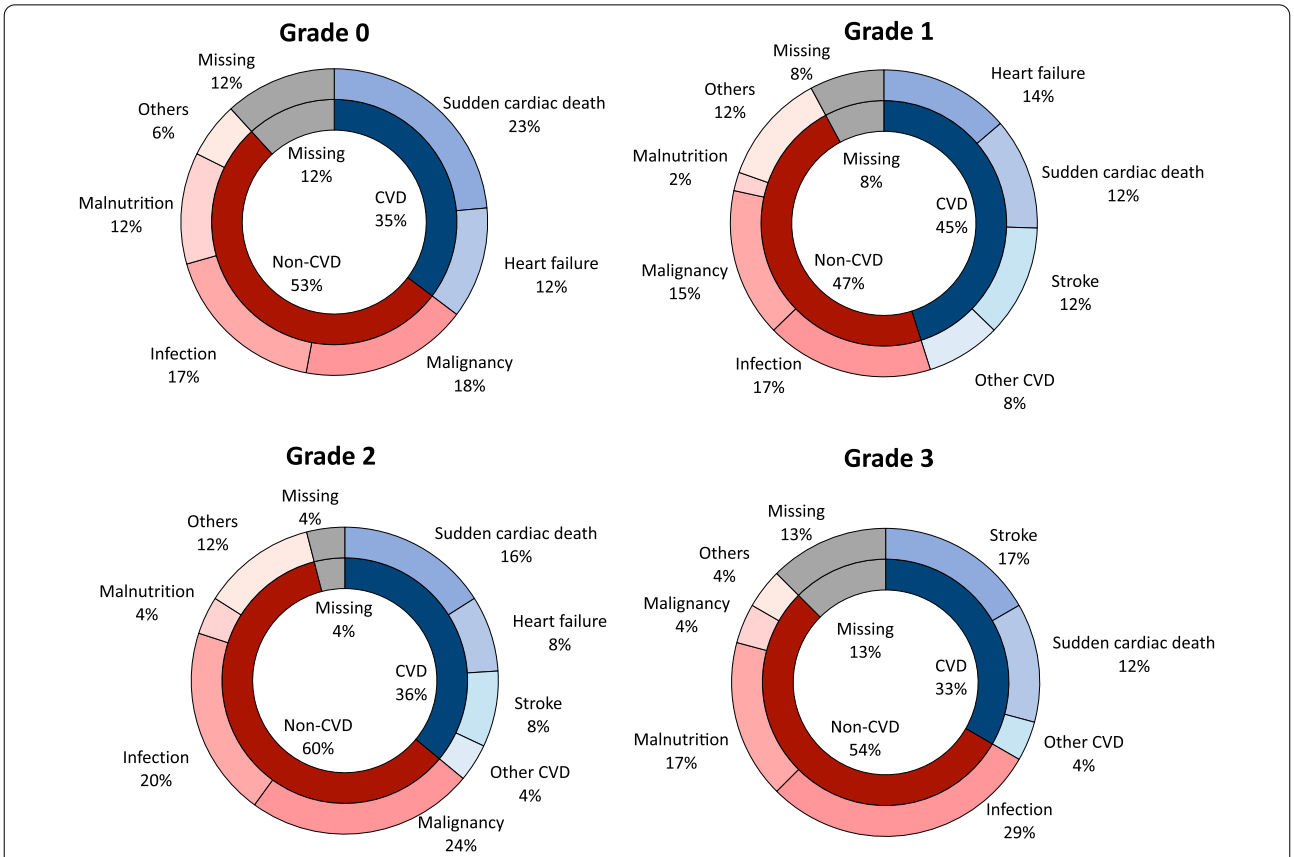

Fig. 2 The causes of death by aortic arch calcification grade. CVD was the most common cause of death among all AAC grades. For CVD death, proportion of stroke increased in higher AAC grades. Non-CVD death accounted for about half of total death. The major causes of non-CVD death were malignancy, infection, and malnutrition. Death of infection and malnutrition increased markedly in AAC grade 3. AAC: aortic arch calcification, CVD: cardiovascular disease

Table 4 Subgroup analysis of causes of death in each grade of aortic arch calcification

	All	CVD	Non-CVD			
			Infection	Malignancy	Malnutrition	Others
All						
Age < 65 y	37 (31.6)	19 (41.3)	7 (29.2)	8 (44.4)	0 (0)	1 (9.1)
≥ 65 y	80 (68.4)	27 (58.7)	17 (70.8)	10 (55.6)	8 (100)	10 (90.9)
Causes of ESKD: DM	50 (42.7)	25 (54.4)	9 (37.5)	6 (33.3)	2 (25.0)	2 (18.2)
non-DM	67 (57.3)	21 (45.7)	15 (62.5)	12 (66.7)	6 (75.0)	9 (81.8)
Dialysis vintage < 7 y	54 (46.2)	21 (45.7)	11 (45.8)	6 (33.3)	4 (50.0)	6 (54.6)
≥ 7 y	63 (53.9)	25 (54.4)	13 (54.2)	12 (66.7)	4 (50.0)	5 (45.5)
Grade 0						
Age < 65 y	6 (35.3)	1 (16.7)	2 (66.7)	2 (66.7)	0 (0)	0 (0)
≥ 65 y	11 (64.7)	5 (83.3)	1 (33.3)	1 (33.3)	2 (100)	1 (100)
Causes of ESKD: DM	11 (64.7)	6 (100)	2 (66.7)	1 (33.3)	1 (50.0)	0 (0)
non-DM	6 (35.3)	0 (0)	1 (33.3)	2 (66.7)	1 (50.0)	1 (100)
Dialysis vintage < 7 y	12 (70.6)	5 (83.3)	3 (100)	2 (66.7)	1 (50.0)	0 (0)
≥ 7 y	5 (29.4)	1 (16.7)	0 (0)	1 (33.3)	1 (50.0)	1 (100)
Grade1						
Age < 65 y	20 (39.2)	12 (52.2)	3 (33.3)	4 (50.0)	0 (0)	1 (16.7)
≥ 65 y	31 (60.8)	11 (47.8)	6 (66.7)	4 (50.0)	1 (100)	5 (83.3)
Causes of ESKD: DM	20 (39.2)	11 (47.8)	3 (33.3)	3 (37.5)	0 (0)	1 (16.7)
non-DM	31 (60.8)	12 (52.2)	6 (66.7)	5 (62.5)	1 (100)	5 (83.3)
Dialysis vintage < 7 y	24 (47.1)	10 (43.5)	3 (33.3)	3 (37.5)	1 (100)	5 (83.3)
≥ 7 y	27 (52.9)	13 (56.5)	6 (66.7)	5 (62.5)	0 (0)	1 (16.7)
Grade 2						
Age < 65 y	6 (24.0)	3 (33.3)	1 (20.0)	2 (33.3)	0 (0)	0 (0)
≥ 65 y	19 (76.0)	6 (66.7)	4 (80.0)	4 (66.7)	1 (100)	3 (100)
Causes of ESKD: DM	13 (52.0)	6 (66.7)	3 (60.0)	2 (33.3)	0 (0)	1 (33.3)
non-DM	12 (48.0)	3 (33.3)	2 (40.0)	4 (66.7)	1 (100)	2 (66.7)
Dialysis vintage < 7 y	10 (40.0)	4 (44.4)	3 (60.0)	1 (16.7)	0 (0)	1 (33.3)
≥ 7 y	15 (60.0)	5 (55.6)	2 (40.0)	5 (83.3)	1 (100)	2 (66.7)
Grade 3						
Age < 65 y	5 (20.8)	3 (37.5)	1 (14.3)	0 (0)	0 (0)	0 (0)
≥ 65 y	19 (79.2)	5 (62.5)	6 (85.7)	1 (100)	4 (100)	1 (100)
Causes of ESKD: DM	6 (25.0)	2 (25.0)	1 (14.3)	0 (0)	1 (25.0)	0 (0)
non-DM	18 (75.0)	6 (75.0)	6 (85.7)	1 (100)	3 (75.0)	1 (100)
Dialysis vintage < 7 y	8 (33.3)	2 (25.0)	2 (28.6)	0 (0)	2 (50.0)	0 (0)
≥ 7 y	16 (66.7)	6 (75.0)	5 (71.4)	1 (100)	2 (50.0)	1 (100)

AAC, aortic arch calcification; CVD, cardiovasucular disease; DM, diabetes mellitus; ESKD, end stage kidney disease; y, year

Values are numbers (percentage for total death).

There are various methods for the evaluation of vascular calcification related to morbidity or mortality. It has been reported that AAC evaluated by coronary computed tomography (CT) and 3D-CT can also predict CV events [20, 21]. In addition, there were several reports that the calcification score on abdominal radiograph can predict CV events [22, 23]. It is necessary to consider a more appropriate evaluation method, including not only predictive hit ratio but also cost and invasiveness.

There are several limitations in this study. Firstly, the AAC grading based on a plain chest radiograph may be biased by the investigators. However, this method is simple and low cost and thus is available in clinical practice. Secondly, we could not exclude the effect of changes in AAC and laboratory data during the study period on all-cause mortality and causes of death. Thirdly, multivariate analysis with malnutrition and infection mortality as an objective variable was not performed due to small

number of samples/events. Thus, we could not rule out the possibility of other factors which may have increased mortality due to malnutrition and infection. In addition, the limited sample size did not allow to perform a multivariate analysis including all potential confounders for all-cause mortality. To minimize the effect of those confounders, we used a backward stepwise method to decrease the explanatory variables. Finally, this study was conducted on patients from two HD clinics in Japan that may limit the generalizability of the study results. Although the baseline characteristics of the patients in this study appeared to be close to the nation-wide Japanese dialysis cohort, our patients were slightly younger, had a longer dialysis vintage, and used more phosphate binders than those of the JSDT population [7].

Conclusions

CVD was the most common cause of death among all AAC grades, although death of infection and malnutrition markedly increased in HD patients with severe AAC. It is important to pay more attention not only to CVD but also to prevention of fatal infection and malnutrition in HD patients with advanced vascular calcification.

Abbreviations

AAC: Aortic arch calcification; CKD: Chronic kidney disease; CT: Computed tomography; CVD: Cardiovascular disease; DM: Diabetes mellitus; ESKD: End-stage kidney disease; HD: Hemodialysis; JSDT: The Japanese society for dialysis therapy.

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Authors' contributions

T.Hashiba and NM designed this study. T.Hashiba, T.Honda, SK, YO, YT, SF, KN, KM, TK, and NM collected data. T.Hashiba performed analysis. T.Hashiba, MT, and NM interpreted the results and drafted the manuscript.

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None.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

The study was conducted in compliance with the Declaration of Helsinki and approved by the ethics committee in the Mitsui Memorial Hospital, Tokyo, Japan (Approved number: C75). The institutional review board waived the requirement for informed consent from the patients according to the Ethical Guidelines for Medical and Health Research Involving Human Subjects in Japan.

Consent for publication

Not applicable.

Competing interests

All the authors declared no competing interests.

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